A COMPARATIVE STUDY ON EVALUATION OF SERUM LDH IN MANAGEMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

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BONAFIDE CERTIFICATE

This is certify that this dissertation entitled **"A COMPARATIVE STUDY ON EVALUATION OF SERUM LDH IN MANAGEMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA"** submitted by **DR.G.MANIMALA** to the Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the requirement for the award of M.S Degree Branch- IV (OTO-RHINO-LARYNGOLOGY) is a bonafide research work carried out by her under my direct supervision and guidance during the tenure of her course in M.S. ENT from May 2016 to April 2018.

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This is to certify that this dissertation entitled "**A COMPARATIVE STUDY ON EVALUATION OF SERUM LDH IN MANAGEMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA**" is a bonafide and genuine research work done by **Dr.G. MANIMALA** in partial fulfillment of the requirement for the degree of M.S Degree Branch- IV (OTO-RHINO-LARYNGOLOGY) under guidance of **PROF.DR. N. DHINAKARAN, M.S. ENT.,** Professor, Department of OTO-RHINO-LARYNGOLOGY .

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DECLARATION BY THE CANDIDATE

I, **DR.G.MANIMALA** declare that, I carried out this work on, **"A COMPARATIVE STUDY ON EVALUATION OF SERUM LDH IN MANAGEMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA"** at the Department of ENT, Madurai Medical College during the period from September 2016 to August 2017. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award degree or diploma to any other University, Board ,either in India or abroad.

This is submitted to The Tamil Nadu Dr.M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the MS DEGREE examination in OTO –RHINO-LARYGNGOLOGY.

Place: Madurai

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CONTENTS

INTRODUCTION

A neoplasm or carcinoma is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues and persists in the same excessive manner after cessation of stimuli which evoked the change[1].

Persistence of cancerous cells, even after the stimuli is removed is due to the heritable genetic change that is passed to tumor cell progeny. The genetic change leads to excess unregulated proliferation, which is also autonomous. All tumor cells have two compartments 1. Proliferating neoplastic cells which is the parenchyma 2. Supportive stroma which is connective tissue and blood vessels.

Head and neck malignancy poses a significant health problem in INDIA .

A] In INDIA population registries estimates annual incidence of 25000 new cases of carcinoma larynx alone .

B] Head and neck malignancies have numerous hidden areas called" coffin corners" where tumor continues to grow.

C] Eventhough premalignant lesions can be clearly identified there is a significant rate of late presentation in our country.

D] Early detection and treatment is the only chance for better outcome as these tumors are aggressive compared to tumors elsewhere.

The importance of early detection will help both in cure and lessening the morbidity, thereby enabling the patients to lead a qualitatively better life.

The need for an easy and simple test that is suggestive of cancer quite early even before the patients become symptomatic and which can be done during routine visits to the health care facility at an affordable cost.

REVIEW OF LITERATURE

The concept of examining apparently healthy people for finding out occult cancer , started with the trial by Pennsylvania chapter of American cancer society in 1920 . Ewing proposed the methods for earlier detection and therapy starting treatment by instituting cancer detection and prevention clinics .

Cancer detection methods include complete

History

Clinical examination

Blood investigation

Diagnostic scopy[video laryngoscopy]

Computerised tomography scan

Molecular mechanism involved in head and neck malignancy has evolved in recent years . A tumor progression from normal epithelial cell into squamous cell carcinoma involves a series of genetic and chromosomal abnormalities.

3 mechanisms involved in carcinogenesis are

A] loss of tumor suppressor genes

B] cellular oncogenes and their products

C] viral oncogenes

TUMOR SUPPRESSOR GENES

These are the genes that play a vital role in controlling cell proliferation . When they get mutated or deleted, tumor cell proliferates[2].

P53

RB GENE

P16 are the genes involved in head and neck squamous cell carcinoma

P53

It is the commonest gene to be involved in head and neck squamous cell carcinoma, located in chromosome 17p,Also called 'GUARDIAN OF THE GENOME'[3]. P53 acts by activating p21 gene which inhibits oncogene CCDNI. It blocks cell division in G1 phase and also promotes apoptosis. The natural function of p53 is to prevent cancers by killing DNA damaged cells. Mutation coupled with over expression of oncogenes like CCDNI results in cancer[4].

RB GENE [RETINOBLASTOMA]

20% of head and neck squamous cell carcinoma have loss of mutation of ch 13q that results in inactivation of tumor suppressor gene[5].

P16 GENE

Located in ch9 it gets inactivated in head and neck squamous cell carcinoma.

CELLULAR ONCOGENES AND THEIR PRODUCTS

Normal cell proliferation and replication requires binding of growth factors to specific receptors that results in activation of cellular processes leading to cell division. These are mediated by G-PROTEINS , TRK-PROTEINS. The genes that control these normal functions are called proto – oncogenes. Cancers result from abnormal activation of these genes by carcinogens. Oncogenes involved in squamous cell carcinoma of head and neck are

1. CCNDI
2. MYC
3. ras

CCNDI

Located in chromosome 11q13 it is found consistently amplified. It can occur along with p53 abnormalities.

MYC

Cellular MYC is a family of regulatory nuclear proteins expressed in 40% of head and neck squamous cell carcinoma[6]. It is more

prevalent in INDIA. It is also expressed in precancerous conditions like leucoplakia.

Ras

Ras family of oncogenes [H,N,K] regulate tyrosine kinase proteins leading to increased cell division. It is found in 40-70% of head and neck squamous cell carcinoma. Ras reflects disordered cell division rather than cancer initiation.

EPIDERMAL GROWTH FACTOR RECEPTORS

Stimulation of these receptors results in increased cell division . These receptors are expressed in large amount in head and neck squamous cell carcinoma.Their levels correlate with prognosis , recurrence and survival rates. Vitamin –A and other retinoids given for chemoprevention act by decreasing these receptors . Anti EGFR monoclonal antibodies are used to reduce the dose of cisplatin in combination chemotherapy[7].

VIRAL ONCOGENES

Human papilloma virus type 16 and 18 and head and neck squamous cell carcinoma has a strong link [8] . The viral DNA is incorporated into host cell genome at locus 29. This causes expression of proteins E6 and E7. They bind and inactivate tumor suppressor gene p53. The HPY-genome have been identified in cells of oral cavity , pharynx and larynx .

Any mass above 1-2 cm diameter requires its own blood supply. Some oncogenes can induce the expression of angiogenesis factors[9].Nitric oxide a key vasoregulatory molecule is a key mediator in angiogenesis of head and neck squamous cell carcinoma. Though many aspects of molecular genetics of head and neck squamous cell carcinoma remains undiscovered, clinical tests to assess prognosis ,early tumor detection and recurrences are done applying the knowledge available. Cytogenetic alterations in diagnosing viral etiology is not done due to expensiveness , time consuming, lack of universally expressed oncogene in head and neck cancers, need sophisticated equipment and tests like PCR , southern blotting etc.

Indian population is largely residing in rural areas and first health worker to come in contact with patient is primary health worker, highly sophisticated tests are not possible in our set up. There is a need for easy detection that can be done cheaply.

Several enzymes[10] can be used in diagnosis of malignant conditions like alkaline phosphatase, acid phosphatase, transaminases , phosphogluomutase.

The following enzymes have been studied regarding head and neck squamous cell carcinoma.

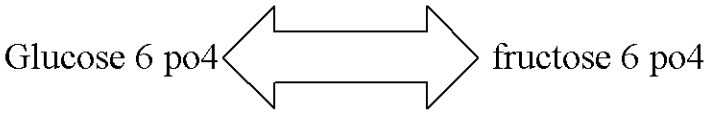
1. Phosphose hexose isomerase

2. Adenosine deaminase

3. Lactate dehydrogenase

PHOSPHOSE HEXOSE ISOMERASE

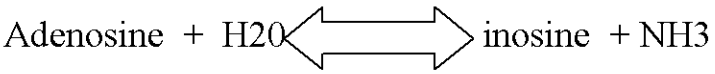
An enzyme of glycolytic pathway. it catalyses conversion of glucose -6-phosphate to fructose-6-phosphate.



It is found in liver and RBC 's 1000 times more than serum.it is elevated in head and neck squamous cell.It plays a significant role in diagnosis of cancers, detection of residual growth , response to treatment and early detection of recurrence and secondary deposits . This enzyme is manually estimated by seliwanoff reaction.

ADENOSINE DEAMINASE

The enzyme catalyses the catabolism of adenosine to inosine and ammonia. Its activity is inversely proportional to degree of cell differentiation.



This enzyme is found mainly in T-lymphocytes and is related to lymphocytic differentiation and proliferation . Its activity is also increased

during rapid proliferation of cells. Its activity decreases in lymphoproliferative and myeloproliferative conditions. The enzyme levels are increased 1-3 fold in head and neck squamous cell carcinoma . Highest level are seen in adenocarcinoma and lymphoma. The level falls dramatically following radiotherapy and or surgery.

LACTATE DEHYDROGENASE

Lactate dehydrogenase oxidizes lactic acid to pyruvic acid using NAD + as co enzyme.It also catalyses the reverse action. Serum LDH level is the combined activity of 5 iso enzymes . LDH – 1 predominates in cardiac muscle , LDH -2 kidneys and brain , LDH 3 in brain and lungs , LDH 5 in liver and skeletal muscles .Normal level ranges from 140 – 280 IU/L. The unit is a electrophotometric measure of decrease in optical density of the test solution in 5 minutes due to oxidation of NADH to NAD+ during which the enzyme catalyses the reduction of 0.1 m sodium pyruvate.

Various isoenzymes of LDH are elevated in certain conditions . LDH -1 is elevated in myocardial infarction . LDH -5 increases in liver disease and progressive muscular dystrophies.

It is also elevated in certain cancers like lymphoma, Ewing sarcoma , and testicular tumours. In these cancers it is used to assess response to treatment , prognosis and early detection of recurrences . Its role

in head and neck squamous cell carcinoma has been evaluated in limited number of studies. They show an increased level in head and neck squamous cell carcinoma.

The levels are high in ulcerative tumors when compared to nonproliferative tumors. The enzyme level correlate with the stage of the disease. stage III and stage IV showing higher levels compared to early cancers. Patients with cervical or distant metastasis exhibit higher values when compared to lesser stages. In all categories patients show fall in level after treatment irrespective of whether surgery / radiotherapy alone or surgery with radiotherapy was used.

In this study LACTATE DEHYDROGENASE is used primarily as it could be tested in laboratory across urban and rural areas alike. The technical staff are more familiar with the testing procedure of LDH as it is routinely estimated for other purposes like myocardial infarction.

For intracellular enzyme to get elevated in serum , there are certain factors which determine its entry .according to BODANSKY, the following factors are the determinant

a) altered enzyme production by tissue

b) blocking normal secretary pathways resulting in regurgitation into serum

c) excretion of enzyme by diseased organ or tissue into blood

d) change in permeability of tissues shows that enzymes leak into serum

e) increased cell death or apoptosis so that enzymes leak from damaged cells into serum or extracellular fluids.

Normal serum levels of intracellular enzymes are produced by routine destruction of cells . Malignancy produces accelerated cell death resulting in raised serum levels of those enzymes. LDH being a component of glycolytic pathway which is the main energy supplier of a cell , might be increased as a result of increased metabolic activity of malignant cells.

AIMS AND OBJECTIVES

1. To assess the efficiency of serum lactate dehydrogenase as a biochemical marker in head and neck squamous cell carcinomas.
2. To assess the tumor burden or load of the patient using serum lactate dehydrogenase levels
3. To assess the response to treatment mostly radiotherapy by checking fall in serum level after radiotherapy.
4. To detect early recurrence in patients treated by radiotherapy as post radiation changes effectively mask clinical examination for recurrences.
5. To compare lactate dehydrogenase levels between various histological types of head and neck cancers.
6. To assess the relationship between serum LDH levels and degree of tumor differentiation.
7. To assess the relationship between serum lactate dehydrogenase levels and morphological type of tumor.

DEFINITION AND NOMENCLATURE

Serum LDH or serum markers in wide term includes markers that are largely selected randomly and are measurable. Leaky capillaries, blood vessels and lymphatics in cancerous cells allow cancer associated molecules to collect into blood and urine .

A serum marker should ideally have high sensitivity and specificity. It is important not to miss a cancer and thus it is better to be wrong on the other side of including those without cancer. The role , type and ease of sample collection and assay depends upon the use of marker . For follow up it is the change in the value of a marker that is important rather than its absolute value . The genome consist of approximately 30000 genes and proteome 300000 proteins. The function of most of it is not understood. Thus markers may only be associated with a tumor, its recurrence or its prognosis without any science linking the disease to the marker .

NOMENCLATURE

Standardized nomenclature is essential to allow assimilation of data from different units and be internationally recognised. INTERNATIONAL CLASSIFICATION OF DISEASE ICD 10. ICD – 10 tumor site codes . The classification of malignancies are broken down into

categories based on point of origin and behaviour . Sites for malignant neoplasms are prefixed by C and sites for *in situ* and benign neoplasms by D. For each anatomical site the initial three alphanumeric code is supplemented by a decimal point and an additional digit to identify subsites 0-7 , an overlapping site 8 or unspecified subsite 9

DATA COLLECTION IN HEAD AND NECK CANCER

Data are collection of readily observed facts and these are need to be stored in a standardized format and content that compromise data base[11]. For standardization data gathering requires underlying skeleton of items ie data set. Collection of data is essential to get a knowledge on malignancies treated , stage distribution , type of treatment , complications of treatment , survival and quality of life measures . Traditional methods of data collection include cancer registries , personal data bases , histopathology records , and patient administration systems .

SURGICAL ANATOMY RELATED TO HEAD AND NECK MALIGNANCY

OROPHARYNX Oropharynx is becoming a common site for upper aero digestive track malignancies .The structure of oropharynx is relatively complex and subdivided into soft palate, tonsil , base of tongue and posterior oropharyngeal wall[12]. Each site has specific characteristics features.

SOFT PALATE : It separates nasopharynx from oral cavity and oropharynx incompletely.It contains levator and tensor palatine, uvular muscle ,palatopharyngeus and constrictor muscles . There are more minor salivary glands within the soft palate and blood supply is by ascending palatine branch of facial artery . Motor supply is by cranial fibres of accessory nerve through pharyngeal plexus of vagus nerve except tensor veli palatine that is supplied by mandibular nerve . Glossopharyngeal and lesser palatine nerve provides sensory innervation .

TONSILLAR FOSSA : It contains palatine tonsil in the space between two pillars, anterior and posterior formed by palatoglossus and palatopharyngeus muscle respectively. It is a lymphoid tissue. ascending pharyngeal artery , branches of facial, lingual and internal maxillary artery provides blood supply. glossopharyngeal and lesser palatine branches of maxillary nerve provides neural supply .

BASE OF TONGUE : Tongue base is rich in lymphatics . It extends from circumvallate papillae to vallecula and glossopalatine sulci laterally. It is rich in lymphatics. Lingual artery – dorsal lingual branch provides blood supply. Hypoglossal nerve provides motor innervation .

POSTERIOR PHARYNGEAL WALL : It extends from region of soft palate to epiglottis and borders tonsillar fossa and pyriform sinus .

The location of oropharynx is between respiratory and digestive tract. the carcinomas in this area will change swallowing , speech and respiration or breathing. Though carcinoma is uncommon but in clinical practice the patient presenting with swelling in this area tends to be malignant.

LYMPHATICS : Oropharynx has a complex lymphatic pattern . Lymphatic spread from oropharynx depends on size and site of malignancy . Level II III IV is the main drainage area for oropharyngeal tumors. Primary drainage is to jugulodigastric nodes and retropharyngeal and parapharyngeal nodes . metastasis involve mid and lower cervical nodes . Skip metastasis is rare .

Tumors of tongue base , soft palate and posterior pharyngeal wall have bilateral lymph node enlargement. Even patients with early T stage will present with higher N stage in oropharyngeal malignancies .

ANATOMY

Oropharynx extension is between hard palate to hyoid bone. anatomical divisions include anterior wall , lateral wall and posterior wall . anterior wall bounded by base of tongue anteriorly – v shaped line of circumvallate papillae. There are lymphoid aggregates here which gives a false impression of early neoplastic lesions. Lateral wall of oropharynx – tonsil , tonsillar fossa , faucial pillars and lateral pharyngeal wall . Lateral to this wall is the parapharyngeal space . Posterior pharyngeal wall extends from hard palate and passavants ridge to hyoid bone there it continues with hypopharynx. Here the mucosa is smooth with minimal lymphoid aggregates. Roof is formed by inferior surface of soft palate and uvula .

Blood supply is from branches of external carotid artery . Nerve supply is through glossopharyngeal nerve and vagus nerve. Hypoglossal is motor to tongue base and trigeminal provides motor and sensory to soft palate.

CLINICAL SIGNIFICANCE

Cranial nerve IX and X also have tympanic and auricular branches that causes referred otalgia in patients with oropharyngeal malignancy . Lymphatic drainage includes upper and middle deep cervical node , retropharyngeal node . Soft palate drains into upper jugulo digastric

node. There is cross over pattern of lymphatic drainage and tumors involving midline structures will have bilateral node involvement . Retropharyngeal and parapharyngeal spaces are two potential spaces related to oropharynx which are of surgical importance.

Pre cancerous lesions tend to occur in oro pharynx[13]. These include leucoplakia, erythroplakia, chronic ulcer / sharp tooth, nicotine mucositis, sub mucous fibrosis. Also suspected lymphocytic lesion like unilateral tonsillar enlargement and bulge in posterior one third tongue should be considered for early detection .

LARYNX

Laryngeal carcinoma is the most common malignancy worldwide. Due to economic development in underdeveloped countries , there is also increased alcohol and tobacco smoking practices . Function of larynx is essential for maintainenance of life quality . Laryngeal cancer has its impact not only on life but also on voice , swallowing and psychology .

ANATOMY

Larynx includes supraglottis , glottis and subglottis[14].

Subsites include

SUPRAGLOTTIS

Suprahyoid epiglottis

Aryepiglottic fold

Arytenoid

Infrahyoid epiglottis

Ventricular bands[false cords]

GLOTTIS

Vocal cords

Anterior commissure

Posterior commissure

SUBGLOTTIS

The larynx also has potential spaces of clinical significance , pre epiglottic and paraglottic spaces, reinke's space and anterior sub glottis wedge, supraglottis is derived embryologically from buccopharyngeal

anlage 3 and 4 arch but glottis and sub glottis are from pulmonary anlage . Therefore each part has independent lymphatic drainage .

LARYNGOPHARYNX / HYPOPHARYNX

It is physiologically a component of upper aero digestive tract. its upper part forma a common pathway for both respiration and deglutition .Therefore tumors of hypopharynx produces both disturbance in swallowing and respiration. Early diagnosis and management is necessary as patient present usually in advanced stage. Tumors of hypopharynx and cervical oesophagus are considered most challenging of upper aero digestive track tumors. Majority are squamous cell carcinoma[15]. They also present at an advanced stage. As with all other malignancies, a multidisciplinary approach is needed for management. The available modalities yield a poor prognosis .

ANATOMY

Three distinct sites

Pyriform sinus

Post cricoid

Posterior pharyngeal wall

PYRIFORM SINUS:

It extends from pharyngoepiglottic fold to upper part of oesophagus. It constitutes anterior , medial and lateral wall that forms an inverted pyramid. Base is at the level of pharyngoepiglottic fold and apex extends just below cricoid cartilage. It is bounded laterally by thyroid cartilage and medially by aryepiglottic fold and arytenoid and cricoid cartilage. These form channels on either side of larynx that open posteriorly . Lateral wall continues with posterior pharyngeal wall and medial wall forms part of aryepiglottic fold that eventually merges with postcricoid mucosa. Superiorly it is bounded by thyrohyoid membrane and aryepiglottic fold lateral and medial aspect respectively. deepest and inferior portion is called apex which is related to thyroid cartilage , cricoid cartilage and para glottic space lateral, medial and inferior aspect.The boundaries of inverted pyramid are base – pharyngoepiglottic fold and apex just below thyroid cartilage. The lower part is lateral to aryepiglottic fold and medial to thyroid lamina .This close association makes tumor spread easily to larynx .the medial pyriform sinus mucosa is the posterior wall of paraglottic space and separated from endolarynx by aryepiglottic fold and lateral cricoarytenoid muscle . Ary epiglottic folds separate endolarynx from medial wall of pyriform sinus which is called MARGINAL ZONE . Though ary epiglottic

fold forms part of supraglottis , tumors from this site are aggressive like hypopharyngeal cancers .

POST CRICOID REGION: extends from arytenoid cartilage to inferior border of cricoid cartilage. It continues thereafter with upper end of cervical oesophagus. It forms the anterior wall of hypopharynx .They commonly invade cricoid cartilage and posterior cricoarytenoid muscle. Due to close association with trachea-oesophageal groove, post cricoid tumors can involve thyroid gland , para tracheal nodes and recurrent laryngeal nerve .

POSTERIOR PHARYNGEAL WALL: extends from hyoid bone or vallecular to inferior border of cricoid cartilage and from apex of one side pyriform sinus to other side. It is a part of hypopharynx lying between two lines projected posteriorly from vocal cords when they lie in cadaveric position .Inferiorly ends at the level of arytenoids and gets separated from pre vertebral muscles by fascial space . It gets separated from vertebral and para vertebral structures by retropharyngeal space . Tumors cross this space and invade pre vertebral tissues .

Hypopharynx is lined by squamous epithelium. Pyriform sinus has a very rich lymphatics and drains into deep cervical chain[16] . Post cricoid region and inferior part of pyriform fossa drains into paratracheal nodes . Posterior pharyngeal wall drains into retropharyngeal nodes.

CROSS SECTION ANATOMY : there are four layers

Mucosa

Fibrous layer

Muscular layer

Fascial layer

MUCOSA : formed by stratified squamous epithelium over loose stroma

FIBROUS STROMA : formed by pharyngeal aponeurosis

MUSCULAR LAYER : composed of posterior cricoarytenoid muscle anteriorly and middle and inferior contrictor muscles posteriorly . Inferior constrictor condenses into cricopharyngeus muscle distally and superior to this there is area of weakness KILLIANS TRIANGLE through which posterior pharyngeal wall tumors extend outside hypopharynx .

FASCIAL LAYER : arises from buccopharyngeal fascia .

Arterial blood supply to hypopharynx is by superior thyroid artery . Lingual and ascending pharyngeal arteries form collaterals and supply this area . sensory innervation passes through glossopharyngeal nerve and vagus nerve to nucleus solitarius in brain stem . The internal branch of superior laryngeal nerve pass through superior part of lateral wall of pyriform sinus and through thyrohyoid membrane to join the vagus. These sensory fibres

synapse with jugular ganglion in jugular foramen along with sensory fibres of Arnold nerve from external auditory canal. This nerve interposition causes referred otalgia in pyriform sinus tumors .

Lymphatic drainage passes from pyriform sinus pass through thyrohyoid membrane to jugulo digastric lymph node and mid jugular and spinal accessory chains . Inferior portion of hypopharynx and post cricoid region drains into para tracheal and para oesophageal nodes and to supraclavicular fossa . Posterior pharyngeal wall drains into retropharyngeal nodes and to mid jugular chain. Cricopharyngeus muscle is the transition between hypopharynx and cervical oesophagus .

Squamous cell carcinoma of hypopharynx is associated with worst prognosis of any head and neck squamous cell carcinoma . 95 % of hypopharyngeal tumors is constituted by squamous cell carcinoma. hypopharyngeal tumors constitute only 3 – 5 % of head and neck malignancy. Less than 40 % of patients survive to 5 years . 30 % of patients diagnosed die within a year of diagnosis .

The causal relationship between alcohol and tobacco , genetic , diet and socio economic status in development of HNSCC also applies to hypopharynx[17]. A condition associated with post cricoid tumor is plummer vinson syndrome or Paterson brown Kelly syndrome. It mainly affects women in about 85 % of cases. This syndrome constitutes combination of

dysphagia, iron deficiency anemia, and oesophageal webs . Chronic irritation progress to webs that result in malignancy . This is mainly due to nutritional deficiency. Studies have shown improving nutritional status and good prenatal care have resulted in decreased incidence of post cricoid carcinoma.

Patients with hypopharyngeal and cervical oesophagus tumor present at an advanced stage. Lesions here will grow unrestricted to larger size since anatomical boundaries of adjacent structures are not limiting likewise in other areas of larynx. This area is also rich in lymphatic drainage and neck mass is a common presentation .

NASOPHARYNX

ANATOMY OF NASOPHARYNX

The average dimensions of nasopharynx in adult are 4 cms high , 4 cms wide, 3 cm length.The posterior wall is about 8 cms from pyriform aperture along the floor of nose. The anterior wall is formed by choanal orifice and posterior margin of nasal septum.The floor is formed by the upper surface of the soft palate which occupies the anterior two third and by the nasopharyngeal isthmus .

The roof and posterior wall form a continuous sloping surface bounded by body of sphenoid, the basiocciput and first two cervical

vertebrae to the level of soft palate. The upper portion of posterior wall lies in front of anterior arch of atlas with a mass of lymphoid tissue embedded in the mucous membrane. The pre vertebral fascia and muscles separate the adenoid from the vertebrae.

The lateral wall is dominated by pharyngeal orifice of the Eustachian tube. It is located in middle of the wall, choana and the floor .The tubal elevation created by the elastic cartilage of the tube is particularly prominent in its upper and posterior lip. Behind the posterior margin of torus between it and posterior wall, lies the lateral pharyngeal recess or fossa of rosenmuller. Aggregates of lymphoid tissue of variable sizes around the tubal orifice and part of the recess are collectively called tubal tonsil .

The fossa of rosenmuller[18] is situated at a corner between the lateral and dorsal walls. Although not obvious in infants the recess can measure upto 1.5 cm in depth in adults. More often than not it appears as a cleft trabeculated at times and recedes posterolaterally to an apex near to edge of the carotid canal opening. It opens into the nasopharynx at a point below the foramen lacerum .

Anatomical relations of the fossa of rossenmuller anteriorly : Eustachian tube and levator palate. Posteriorly: pharyngeal wall mucosa overlying the pharyngobasilar fascia and retropharyngeal space containing the lateral retropharyngeal lymph node of rouviere.

Medially the nasopharyngeal cavity. Superiorly: foramen lacerum and floor of the carotid canal.

Posterolateral (apex) : carotid canal opening and petrous apex posteriorly, foramen ovale and spinosum laterally

Laterally: tensor palate and the mandibular nerve and the prestyloid compartment of the parapharyngeal space. The fossa forms the medial border of the most superior part of the parapharyngeal space.

As the superior constrictors does not reach the base of the skull a lateral gap is (sinus of Morgagni) is created. This gap is bridged only by the pharyngobasilar fascia. Through this, the Eustachian tube with its two muscles one on each side enters the nasopharynx. Along the inferior border of the two muscles the fossa of rossenmuller is separated from the parapharyngeal space by mucosa and the pharyngobasilar fascia. Thus tumour can easily infiltrate and breach this area to spread into the parapharyngeal space.

The blood supply of the nasopharynx is from the ascending pharyngeal branch of the external carotid and palatine branches which pass the superior constrictor supply the pharyngotympanic tube.The nasopharynx is drained by the pharyngeal plexus of veins.

The nerve supply is from branches of the maxillary division of the fifth nerve, glossopharyngeal nerve and branches from the sphenopalatine ganglion. The motor supply of the palatal muscles is from the pharyngeal plexus and partly by the third division of the fifth nerve.

The lymphatic drainage is from an extensive submucosal plexus to the lateral and medial retropharyngeal lymphnode which drain into the upper deep cervical lymph node

CARCINOGENESIS

Carcinogens cause susceptible cells to undergo malignant transformation and develop into malignant growth. two stages of carcinogenesis are there .

INITIATORS : Carcinogens that act in the early phase are known as initiators [19].

PROMOTERS: Act during late stage . a particular carcinogen may act as both initiator and promoter at different times. Moolgavkar and Knudson described a model which incorporated transition of target stem cells into cancer cells. They hypothesize that target stem cells exposed to a carcinogenic event divide into intermediate cells whose rate of differentiation and death is improperly controlled . It is at that stage that

promoters or inhibitors exert their effect, facilitating or inhibiting the transition of intermediate cells to cancer cells .

SURGICAL PATHOLOGY

OROPHARYNX

Three types of tissue are present within oropharynx so as the malignancies squamous cell carcinoma, lymphoma and minor salivary gland tumor. Squamous cell carcinoma is most common malignancy comprising 90% of all malignant lesions. Other types are lymphoma , lymphoepithelial carcinoma , minor salivary gland tumor and malignant melanoma .

Traditional oropharyngeal carcinoma has some difference when compared with HPV associated oropharyngeal carcinoma . Features of traditional oropharyngeal malignancies are as follows

1. >60 years , male preponderance
2. Tobacco and alcohol
3. P16 inactivation
4. Keratinising squamous cell carcinoma
5. Well to moderate to poorly differentiated
6. Nodes less bulky
7. Higher local recurrence

8. 20% chance of distant metastasis

HPV associated oropharyngeal squamous cell carcinoma

1. 40-60 years , male predominance
2. Reduced or no addiction , immoral behaviour
3. P16 over expression
4. Non keratinising
5. Poorly differentiated
6. Small or unknown primary with bulky , cystic or multiple nodes
7. Infrequent local recurrence
8. 5 – 12 % distant metastasis

SQUAMOUS CELL CARCINOMA : Tobacco and alcohol are traditional and synergistic risk factors for oropharyngeal squamous cell carcinoma .There is a relative risk of 70 – 100 % for increased consumption level . There is a super multiplicative effect for both tobacco and alcohol . As concerned with oropharyngeal malignancy smokeless tobacco is a major risk factor[20] . 50 % 0f males and 90 % of females in INDIA acquire oropharyngeal carcinoma by chewing tobacco. These are exogenous risk factors attributed to malignancy . DNA repair , Differences in mutagen

sensitivity , alteration of genes [EGFR] have impact on head and neck malignancy .

Staging is based on tumor size which includes T1 tumor size 2 cm or less , T2 more than 2 and less than 4 cm , T3 more than 4 cm , T4 invades adjacent structures like pterygoid muscles , mandible , hard palate , deep muscles of tongue, larynx .age of the patient, general condition . TNM status , tumor depth, histology, vascular invasion, perineural invasion , previous treatment determines the prognosis. One in three patients also present with second primary therefore it is important to search for synchronous second primary if contralateral nodes are present. Distant metastasis are seen in 8 percent of patients.

CLINICAL PRESENTATION :

1. Dysphagia
2. Pain
3. Foreign body sensation
4. Oral bleeding
5. Referred otalgia
6. Neck mass

Patients present at advanced stages . Psychological and social factors, fear and denial along with late presentation and non specific symptoms lead to delayed presentation . Different clinical presentation and pattern of spread needs different considerations regarding treatment .

The most common site of oropharyngeal squamous cell carcinoma is palatine tonsil and anterior tonsillar pillar .

SOFT PALATE TUMORS : Soft palate malignancies are generally seen on ventral surface . So these can be detected with ease. It may extend into tonsil , retromolar trigone or nasopharynx with involvement of level II node.

LATERAL WALL : Tonsillar fossa presents as foreign body sensation , ear pain and or impaired jaw mobility due to infiltration of periosteum of mandible or pterygoid muscles . If tumor extends into parapharyngeal space there will be involvement of cranial nerves IX X XI XII and sympathetic chain .Level II III IV and retropharyngeal nodes will be involved

TONGUE BASE: These tumors are difficult to detect hence they are detected at an advanced stage only. Due to late clinical presentation which is due to paucity of nerve endings. Lingual tonsil and submucosal location of lesion also adds to this delayed diagnosis. There is increased frequency of

bilateral metastasis due to rich lymphatics and also being a midline structure .Ipsilateral nodal involvement in 70% of cases.

DIAGNOSTIC EVALUATION :

1. Physical examination
2. Imaging
3. Endoscopy
4. Biopsy
5. Frozen section

Complete evaluation of head and neck to exclude synchronous malignancy is important as regards to any head and neck malignancy . Positron emission tomography PET with CT can help in diagnosis of synchronous primary and distant metastasis. PET – CT is more accurate even after 3 months following radiotherapy. Ultrasonogram has proved effective in sensitivity and specificity in neck node imaging than CT and PET – CT. HPV tumors showed intranodal cystic degeneration in ultrasonogram . Pan endoscopy done under general anaesthesia is important to detect lesions , define extent and biopsy and to rule out second primary . Imaging is also done for metastatic cancers of lung , liver , skeletal system and brain .

LARYNX

85 percent of laryngeal tumors are malignant and are moderate or well differentiated. As with other tumor males outnumber females . Macroscopically they may be exophytic or endophytic. Microscopically prickle cells and keratin pearls are present. the staging of laryngeal tumors TNM staging[21] includes T1 includes tumor confined to one subsite with normal vocal cord mobility , T2 extends to adjacent site , T3 limited to larynx with vocal cord fixation , T4 invasion of thyroid cartilage and or extension beyond larynx ,soft tissues of neck , oesophagus , pre vertebral space , encase carotid artery. Transglottic cancer is spread both superficially and into paraglottic space to span all three laryngeal subsites .

HYPOPHARYNX

Almost all tumors are squamous cell carcinoma . Pyriform sinus constitutes largest part , among which medial wall tumors are extensive . TNM staging includes T1 tumor limited to one subsite and 2 cm or less in dimension , T2 invades more than one subsite , not more than 4 cm , T3 more than 4 cm with fixation of hemilarynx, T4 invasion of adjacent structures thyroid , cricoid, carotid artery, soft tissues of neck, pre vertebral fascia and or oesophagus .

ETIOPATHOGENESIS

Head and neck cancer is more common in tobacco users especially males who are between 50 – 60 years .

Tobacco and alcohol play a very great role in etiology of head and neck cancer . They act both independently and synergistically. There exists a dose dependent relationship between smoking and incidence of head and neck malignancy . Quiting smoking reduces the risk but at the same time heavy smokers who had quit smoking even 10 years back had a persistent 3 fold risk of developing laryngeal cancer . Quality of tobacco also determines the risk . Light tobacco is flue cured and dark one is processed by air . There is 5 times increased risk of cancer with use of dark tobacco .

There is many ways of tobacco use. One form is PAN which consist of betel nut , catechu , tobacco and areca nut. It has lead to increased incidence of malignancy of oral cavity and hypopharynx. Tobacco smoke has around 4000 chemicals in it. 43 have been identified as carcinogens. they include polycyclic hydrocarbons , nitrosoamines, polonium -210 which is radioactive . Head and neck malignancy has also strong association with type of tobacco use like smoking , reverse smoking and chewing . More than tobacco , cannabis smoking has a higher incidence of head and neck

squamous cell carcinoma .This is due to the increased concentration of aromatic concentration and higher tar concentration .

Alcohol use though as such it is not a carcinogen , synergistic effect between tobacco and alcohol potentiate carcinogenesis. Ethanol is a solvent which increases the contact time of tobacco related carcinogens with the aero digestive tract mucosa. Ethanol also interferes with retinoids synthesis which is protective in HNSCC. Studies have shown nitrosoamines are in higher concentration in beer, lower in distilled spirit and very less in wine. Resveratrol present in grape and wine has chemopreventive action . this leads to a conclusion that not the total consumption of alcohol determines the risk but the type of beverage used. The risk depends on degree of exposure, duration, intensity and inherent susceptible nature of the individual .

HPV human papilloma virus has also been considered a risk factor in HNSCC[22] . High risk types are 16 , 18 and medium risk types 31 , 33 and low risk types are 6 and 11. Respiratory papillomatosis caused by low risk types has risk of transformation of verrucous squamous cell carcinoma . Epstein – Barr virus is closely associated with nasopharyngeal carcinoma and it has been proven with antibody titres and EBV DNA demonstration in tumor cells .

Environmental factors also play an important role in development of head and neck malignancy . Radium watch dial painting and thorotrast ingestion cause paranasal sinus malignancy and also radiation exposure .

Occupational exposure to hard wood and soft wood has also been implicated in HNSCC . Nickel and chromium refiners are also susceptible to squamous malignancy of larynx .

Dietary factors like iron deficiency in female makes them prone for post cricoid malignancy. Paterson brown Kelly syndrome can be reversed with iron replacement and vitamin B therapy. Salted fish diet which is rich in nitrosoamines has lead to nasopharyngeal malignancy in Chinese population.There is inverse relationship between increased consumption of fresh fruits and vegetables [not contaminated by increased use of pesticies] and development of head and neck malignancy. Similarly dietary carotenoids also protective. Vitamin A has a protective role in development of epithelial tumors by controlling cell differentiation .

Genetic variations also have role in development of cancer . Progressive loss of control over cell growth and death is determined partly genetically. 30 trillion cells in human body are controlled by the known 40 proteins that regulate cell cycle. Genetic alteration accumulate progressively called as multi step carcinogenesis. Interindividual difference in

susceptibility to carcinogen exposure determined by molecular or genetic determinant favours monitoring patients at risk of developing head and neck cancer .

INVESTIGATIONS

CT

MRI

Ultrasound

Radionuclide scanning

FNAC

Pathology

Open biopsy

Sentinel node biopsy

CT :- detects malignant cervical lymphadenopathy in neck

- more exact than clinical examination.

-is fast , easily available and relatively cheap method for head and neck imaging[23].

- Sensitivity of CT IS 84% and specificity 83%

- but physical examination sensitivity 74% specificity 81%.

-normal cervical lymphadenopathy is 3 mm to 3 cm but studies show nodes greater than 1 cm in size on CT scanning may have metastatic disease .

-NODES SUSPICIOUS ON CROSS SECTIONAL IMAGING :

Size greater than 1 cm

Rim enhancement following i.v contrast

Central necrosis

Spherical shape .

- The centre is necrotic and there is a thin rim of inflammation

- Non malignant cervical lymphadenopathy is 3 mm upto 3 cm.

- Current study - all nodes greater than 1 cm size contains tumour except those in low level II, high level III when a 1.5 cm size criteria is used

- Residual and recurrent disease following surgery and irradiation and low volume disease are most difficult to recognise.

- 8mm cervical lymphnode can be missed in CT, it may have 10^8 malignant cells therefore CT cannot be relied fully and elective neck treatment should be considered wherever applicable.

-patient is made to lie supine with head in neutral position for the hard palate to be perpendicular to top of the table. The plane of CT is parallel to

inferior orbitomeatal line . I.V contrast helps in differentiating nodes from vessels . CT is used to evaluate bony destruction.

Normal lymph nodes are well defined round or oval shape , attenuation is similar to muscle.size is an essential determinant for normal nodes in CT and MRI . Nodes more than 1 cm and axial diameter 10 mm are abnormal . For jugulodigastric node alone 1.5 cm length and axial diameter 11 mm should be considered . The ratio of length to transverse diameter is oval for reactive nodes , but for malignant nodes it will be rounded .

Nodal staging is an essential component in treatment of head and neck malignancy . 7 -9 % of nodes positive are detected in those who are clinically negative . Size , shape and presence of central necrosis is essential in diagnosis of squamous cell nodal disease. Central necrosis is most reliable indicator of malignancy. Extracapsular nodal spread implies poor prognosis . CT shows enhancing rim with which is thickened and infiltrating into adjacent fat .

MRI

MRI has better soft tissue resolution and tumor muscle interface when compared with CT and superior to CT for imaging skull base , salivary glands, oral cavity and nasopharynx.Its disadvantages include long

acquisition time of scans with degradation of images due to motion artefact from breathing, swallowing and vascular pulsations. Claustrophobia , cochlear implant , cardiac pacemakers , aneurysm clips and metal within eye are contraindications .

Normal nodes are similar signal intensity to muscle on T1W and slightly higher signal on T2W. Reactive nodes are homogenous low signal on T1w and high signal on T2W.Malignant nodes have heterogenous signal on both T1W and T2W .True necrosis is low signal on T1W and high signal T2W.

ULTRASOUND: High resolution B –mode ultrasound is rapid and inexpensive way to examine neck and also to find out palpable nodes and to take biopsies. High resolution transducers 5 and 20 MHz are used. Usual frequency 5-12.5 MHz with axial resolution of 0.5 mm and lateral resolution of 1 mm . It is useful in assessing invasion of carotid artery and jugular vein by lymphnode metastasis.

Normal nodes are echogenic and mimics fat surrounding it , need high frequency 13 MHz probe for viualization. Pathological nodes are larger with decreased echogenicity due to tumor infiltration , hyperplasia of lymphoid follicles . Power Doppler sonography help to differentiate metastatic and reactive nodes . Contrast agents helps to see intranodal vessels in nodal hilus . Nodal metastases are secondary to squamous cell carcinoma and are

hyperechoic . Sensitivity of ultrasound to diagnose nodal metastases is 75 – 92 % , specificity is 63 – 91 % . Shape is important to diagnose metastatic disease . Vascular infiltration by malignant nodes is rare , seen in 5 % and can be seen in ultrasonogram.

RADIONUCLIDE IMAGING: PET is a technique that map functional and metabolic activity before structural changes take place .PET uses either 18 – FDG or 11 c – methionine can differentiate malignant from normal tissue based on glycolysis or aminoacid metabolism by tumor cells . This is used to identify tumors in normal sized lymph nodes, to differentiate sinus malignancy from secretion, to differentiate fibrosis and tumors. PET is used to stage the primary squamous cell carcinoma along with nodal involvement and distant metastases and for detection of recurrent tumor. PET is superior to both MRI and CT for detection of cervical node metastases. PET is most sensitive method to detect recurrence following radiotherapy. Advantage of PET is to assess recurrence, there may be false positive due to inflammation, to do whole body scanning to identify synchronous primary tumor, distant metastases and to find out site of primary .Disadvantage is lack of availability and space constraint . 6 hours fasting is essential before PET .

- gallium 67, technetium 99 dimercaptosuccinic acid (pentavalent DMSA) are used to detect metastatic lymphadenopathy.

-PET scan assess metabolic activity of cervical lymph node using 18 fluorodeoxyglucose (FDG). Currently CT / PET scan with anatomical localisation is for diagnosing occult primary and for assessing residual and recurrent disease following surgery and irradiation.

FNAC – it is done on a palpable node and useful to assess palpable node when searching for primary.

LYMPH NODES OF HEAD AND NECK :

Divided into 3 systems

1.waldeyers internal ring

2. superficial lymph node system – waldeyers external ring

3.deep system (cervical lymph nodes proper)

Levels of lymph nodes based on MEMORIAL SLOAN KETTERING HOSPITAL PUBLICATION-echelon sites for metastases from head and neck primary sites .

Level 1 : submental and submandibular

Level 2 : upper jugular node

Level 3 : middle jugular node

Level 4 : lower jugular node

Level 5 : posterior triangle

Level 6 : anterior compartment

Level 7 : upper anterior mediastinum .

Totally there are 500 lymph nodes in body and of these around 200 are in head and neck region . The spread of disease from primary tumor to regional lymph nodes occurs by passive transport within lymph .

MANAGEMENT :

1. **SURGERY**
2. **RADIOTHERAPY**

1. SURGERY

OROPHARNGEAL MALIGNANCY :

Per oral

Mid line or paramedian mandibulotomy

Lateral mandibulotomy

Mandibulectomy

Suprahyoid pharyngotomy

Lateral pharyngotomy

TUMORS OF HYPOPHARYNX :

Endoscopic excision : laser or diathermy

Partial pharyngectomy

Partial pharyngectomy and supraglottic laryngectomy

Total laryngectomy and partial pharyngectomy

Total pharyngectomy

Total pharyngolaryngooesophagectomy

TUMORS OF LARYNX:

Microendolaryngeal and laser surgery

Hemilaryngectomy(vertical partial resection)

Horizontal partial laryngectomy

Supracricoid laryngectomy with cricohyoidoepiglottoplexy

Near total laryngectomy

Total resection.

2. RADIOTHERAPY

The last few years showed rapid development in non surgical modalities for HNSCC. Historical treatment included radiotherapy dose fractionation schedule, five days per week for 3 to almost 7 weeks.

Subsequent fractionation schedule includes from 50 Gy# over 3 weeks through 55 Gy in 20# over 4 weeks to 66 Gy in 33 # over six and half weeks. Biological factors influence the response of normal tissue and tumours to radiation therapy. These biological factors are under research to increase the narrow therapeutic ratio between normal tissue damage and tumour. Repopulation of normal and tumour cell clonogens occurs during radiotherapy. During each treatment episode, only a portion of tumour clonogenic cells will undergo lethal damage, the remaining surviving cells will divide and multiply. Complete eradication of tumour cells will be possible only and successful when all tumour cells have been eliminated until which time tumour cells repopulate. There are evidence that repopulation of cancer cells occurs during fractionated radiotherapy, this is more after first four weeks of treatment.

Normal tissue react to ionising radiation in the following ways. That may be early and late[25]. Early reactions are mucositis, loss of taste, skin erythema and skin desquamation. Early reactions occur within first few weeks of fractionated radiotherapy. Late tissue reactions occur after 3 months, causes tissue fibrosis or radionecrosis. Multiple fractions per day lead to shorter inter fraction interval. Therefore sufficient time is needed for normal tissue repair (minimum six hours) but central nervous system requires long duration.

METASTATIC NECK DISEASE Nodal metastasis (metastatic neck disease) is an important prognostic factor in head and neck cancer[26]. There are no primary lymphatics for tumour. Cancer cells gain access to lymphatics from periphery of the tumour through gaps between lymphatic endothelial cells. Tumour spread occurs from primary tumour to regional lymph nodes by passive transport within lymph. The afferent lymphatics join the marginal sinus in the cortex of lymph nodes where cancer cells may lodge.

Growth patterns of squamous cell carcinoma within cervical lymph nodes. Extra nodal extrusion of tumour is by destruction of capsule and direct penetration. Growth within affected node occurs to a reasonable extent before extranodal spread. Extra nodal spread occurs early in genesis of tumour growth within the node.

Deposition of malignant embolus within subcapsular sinus along with simultaneous arrest of tumour within capsular or juxtacapsular lymphatics.

Extranodal spred can occur much earlier. This is by capsular or juxtacapsular emboli with no intranodal cancer[27].

Stages of metastasis in lymphatics[28]:

PRE METASTATIC INVASION OF EPITHELIAL BASAL LAMINA OF PRIMARY TUMOUR

ENCROACHMENT

PENETRATION

TRANSLOCATION OF CELLS THROUGH LYMPHATICS

INTRA NODAL SETTLING

PROLIFERATION AND DESTRUCTION OF LYMPH NODE

Cancer cells can reach blood stream by various other routes. They are directly from node or collaterals by passing the lymphnodes. This leads to skip metastases[29]. It is also deficient to differentiate whether metastases occurred through blood or lymphatic channels. Whether tumour growth is more than 0.1 – 1 mm size, tumour vascularisation occurs followed by increased vascular invasion.

The presence of regional lymph node indicates the tumour is capable of metastasing locally and at distant sites. The degree of lymph

node involvement is an indirect index of systemic tumour burden. Based on this, staging procedure is done by removing regional lymph nodes.

MOLECULAR METHODS OF DETECTION OF METASTASIS[30]

This is 500 times more sensitive than histological method of cancer detection. Phage clone technique identified tumour specific p53 mutations in 6 of 28 lymphnodes. Oligonucleotide mediated mismatch ligation assay is new and highly sensitive and has been demonstrated in detection of cancer cells in histologically negative regional lymph node in lung and colorectal cancer.

OCCULT NECK DISEASE

Occult neck disease has the potential to manifest as clinical disease. Patients with micro metastasis tend to be 3 times more curable than with macroscopic evidence of disease.

TUMOUR METASTASIS

It involves interaction between tumour and its host and influenced by humoral, endocrine, cellular, metabolic and nutritional factors[31]. Metastasis involve release of cells from primary tumour and dissemination to distant sites, get arrested in microcirculation of organs, extravasation and infiltration into organs. There is a strong correlation

between tumour metastases (spontaneous) and high levels of type IV collagenase

Factors that indicate poor prognosis of cervical lymph nodes are site, size, number, level, extracapsular extension, morphology, laterality

Clinical examination is important to assess lymph node

TREATMENT OF METASTASES

Presence of cervical lymphadenopathy has adverse effect on survival .

No NECK :

Elective surgery

Elective radiotherapy

Elective neck investigation – CT / MRI

Wait and watch

There is more chances of subclinical disease in neck especially squamous cell carcinoma of oral cavity , pharynx and supraglottis .The likelihood of nodes being involved depends on size , site and histological differentiation[32]

INDICATIONS FOR ELECTIVE NECK TREATMENT :

-more than 25% chance of subclinical disease in neck

-regular follow up not possible

-difficult clinical evaluation

N2a and N2b NODES:

-radical /modified radical neck surgery

Post operative radiotherapy

N2c NODES:

-seen in tongue base , supraglottis and hypopharynx

-surgery followed by post operative radiotherapy .

CONTRAINDICATIONS TO NECK DISSECTION :

-untreatable primary

-unfit for surgery

-inoperable neck disease

-distant metastases

QUALITY OF LIFE IN HEAD AND NECK CANCER

Generally for cancer patients, the quantity of survival is of prime importance. But quality is also to be considered when we decide a particular treatment modality. It is determined by chances of survival and outcomes compared to other available treatment options. Quality of life is important in head and neck cancer patients due to difficulties encountered in day to day life. Physical function, psychological state, social interaction, somatic sensation and symptoms are the main components of quality of life[33]. Economic, occupational and family domains are also included.

Patients treated with surgery had greater dysfunction when compared with post radiotherapy patients. But both have similar global QC scores. For advanced head and neck cancer, palliation is more important. World health organisation states that palliative care offers support to family to cope during patient illness, integrates physical, social and psychological aspects, provides pain relief. Pain relief is by analgesics- primary and secondary.

Primary analgesics have direct blocking effect on pain. They are non opioids- paracetamol, NSAIDS. Codeine and morphine are first choice in cancer pain. Secondary analgesics relieve pain by reducing peri tumour edema, reduce inflammation, block neuropathic pain, reduce muscle colic and metastatic pain.

Nausea and vomiting are common problems in majority of cancer patients. Anti emetic drugs commonly used are cyclizine, haloperidol, metoclopramide, dexamethasone. There are certain medical negligence encountered in head and neck surgery. Perioperative problems, delayed diagnosis, problems due to systems failures like pathology, imaging, endoscopy, operative problems like accessory nerve damage, recurrent laryngeal nerve damage, facial nerve paralysis, vagal injury, vascular injury, airway problems, laryngeal and oral cavity problems.

MATERIALS AND METHODS

A total study of 50 proven cases of head and neck squamous cell carcinoma done in department of ENT, Government Rajaji Hospital , Madurai, Tamilnadu during the period from September 2016 to August 2017. Age and sex incidence, various presentations, symptomatology and serum values of patients pre treatment and post treatment are well documented. Treatment modalities adopted are radiotherapy and surgery. Among the 50 cases, only 3 cases underwent total laryngectomy and remaining 47 were subjected to radiotherapy.

The clinical study includes 50 patients attending department of OTORHINOLARYNGOLOGY and surgical oncology and radiotherapy, Government Rajaji hospital Madurai. The approval of the Institutional review board was obtained.

Inclusion Criteria

Age $\geq$ 30 years

Histologically proven to be carcinoma of head and neck

Consent and willingness for participating in study

Exclusion Criteria

age < 30 years

carcinoma of skin and thyroid

any co-morbidity

lymphoma

any other primary carcinoma or on treatment for any other malignancy

minor, prisoner,pregnancy

carcinoma in situ

patients who are considered to meet the criteria of mental incapacity

The study design is a case control study. the patients are divided into two groups.

A] controls

B] cases

CONTROLS

The control group consists of 50 age matched individuals of both sexes. The control group consists of patients attending ENT OPD for problems not related to cancer. A brief clinical history and gross physical examination was done to exclude cardiac and liver disease in control group. no blood investigations other than serum lactate dehydrogenase was done in this group. Serum lactate dehydrogenase levels were taken during first visit and was not followed up with similar estimation.

STUDY GROUP [CASES]

The study group consisted of 50 cases of histologically confirmed head and neck squamous cell carcinoma . A thorough history and meticulous physical examination was done in all patients including indirect laryngoscopy examination and direct laryngoscopy examination.

Routine blood investigations like total count , differential count , haemoglobin % erythrocyte sedimentation rate, blood urea, sugar and serum creatinine levels were done in all patients. Urine was tested for albumin , sugar and deposits.

Radiological examinations like x-ray chest to rule out pulmonary secondaries, ultrasonogram to assess liver function and to rule out hepatic secondaries were done in all patients.

Computerized tomography was done in appropriate cases to assess the extent of tumor , to note involvement of clinically silent areas like pre epiglottic, para glottic spaces etc and to pick up clinically silent neck nodes. Magnetic resonance imaging was not done due to cost constraints.

All patients were subjected to pharyngolaryngoscopic examination under local anaesthesia and an accurate evaluation of tumor evaluation according to TNM staging, done by fibre optic Hopkins rod telescopes. Photo documentation was done in selected cases. Biopsy taken from tumor and sent for histopathological examination.

After a complete clinical and radiological evaluation patients were subjected to radiotherapy except for 3 patients who were treated by surgery. Patients requiring chemotherapy were not included in the study.

For all patients receiving radiotherapy serum levels were sampled before initiation of radiotherapy and then again on completing radiotherapy .For patients treated by surgery serum levels were taken before surgery and 2 weeks after surgery.

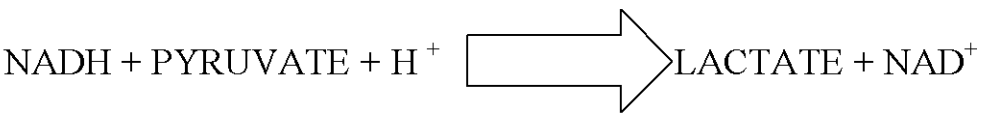
METHOD OF COLLECTION AND ESTIMATION

COLLECTION

As the levels of LDH can be elevated following strenuous physical activity the samples were collected after a period of rest in a relaxed supine patient, from a peripheral vein 3 ml of blood was collected into a sterile , clean ,dry container[34]. Care was taken to avoid hemolysis during sampling , collection and transportation as hemolysed sample can give high values[35].

ESTIMATION

Estimation was done immediately once the blood sample clotted as the level of enzyme falls in a stored sample. The clotted blood was centrifuged at 3000 rpm. The clear supernatant containing serum was used for the test. The procedure was perfomed in auto analyser using LDH KIT[36].



OBSERVATION

In this study of 50 cases of head and neck squamous cell carcinoma who attended and got treated at Govt Rajaji Hospital Madurai , the following observations are made.

	SEX	NUMBER	PERCENTAGE	AVERAGE AGE IN YEARS
CASES	MALE	46	82%	60
	FEMALE	4	8%	47
CONTROLS	MALE	40	80%	58
	FEMALE	10	20%	50

The study group consist of 50 cases of 46 males and 4 females , average age for males 60 years and for females 47 years.

The control group consist of 50 cases of 40 males and 10 females , average age for males 58 years and for females 50 years.

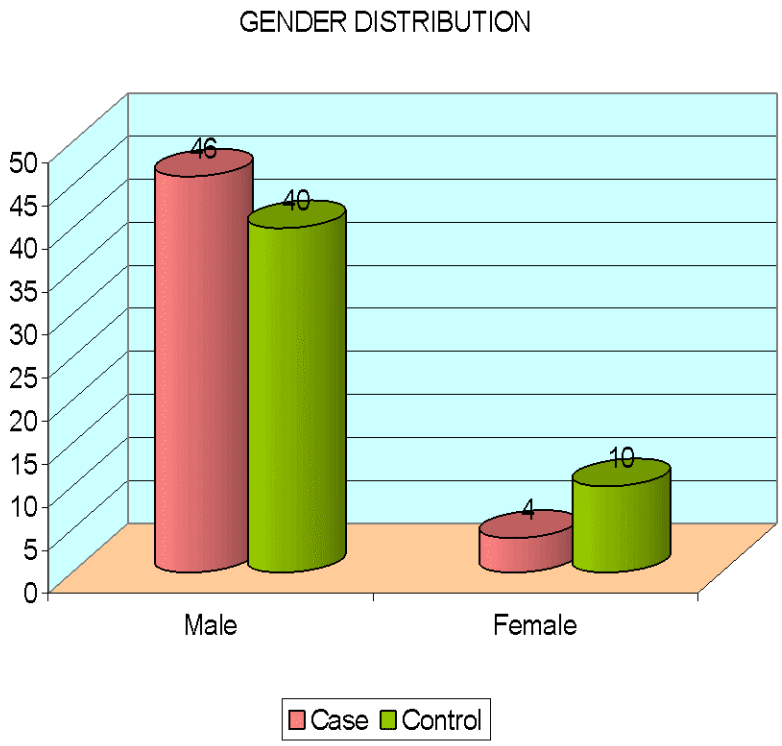

GENDER DISTRIBUTION
50
45
40
35
30
25
20
15
10
5
0
46
40
4
10
Male
Female
Case
Control

TABLE 2

CONTROL GROUP	NUMBER	MEAN AGE IN YEARS	MEAN SERUM LDH IN IU/L
MALE	40	58	236
FEMALE	10	50	198

The control groups exhibited a mean serum LDH level of 236 IU/L for males and 198 IU/L for females

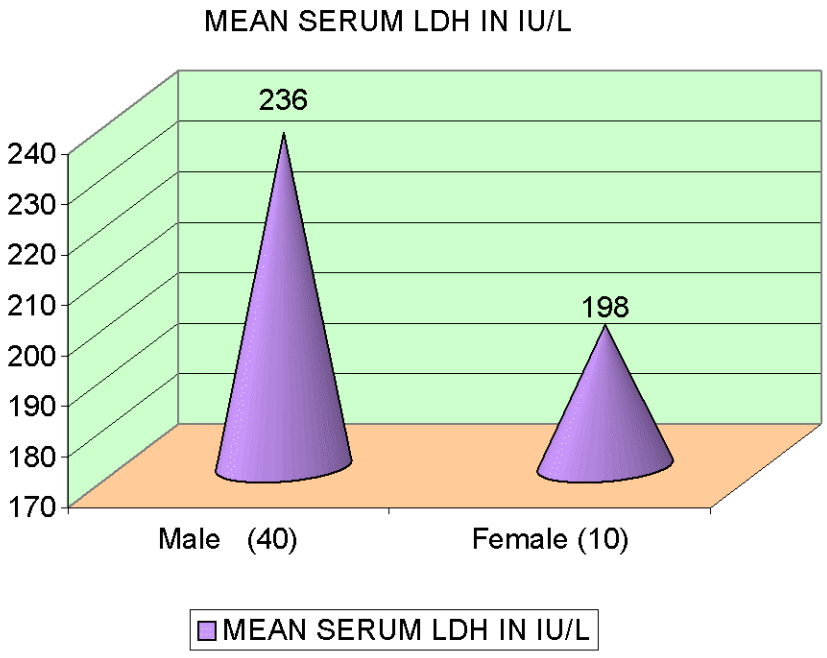


TABLE 3

SITE/REGIONAL DISTRIBUTION	TOTAL NUMBER	MALE	FEMALE	PERCENTAGE
SUPRAGLOTTIS	20	19	1	40%
GLOTTIS	11	11	0	22%
SUBGLOTTIS	1	0	1	2%
HYPOPHARYNX	8	7	1	16%
OROPHARYNX	10	9	1	20%

In the study group of 50 cases , 60% had supraglottic carcinoma , 22% had glottis carcinoma, 2% had subglottic carcinoma, 20 % had hypopharyngeal malignancy and 20% had oropharyngeal malignancy . Males outnumbered females in all categories except in subglottic category all groups had male patients.

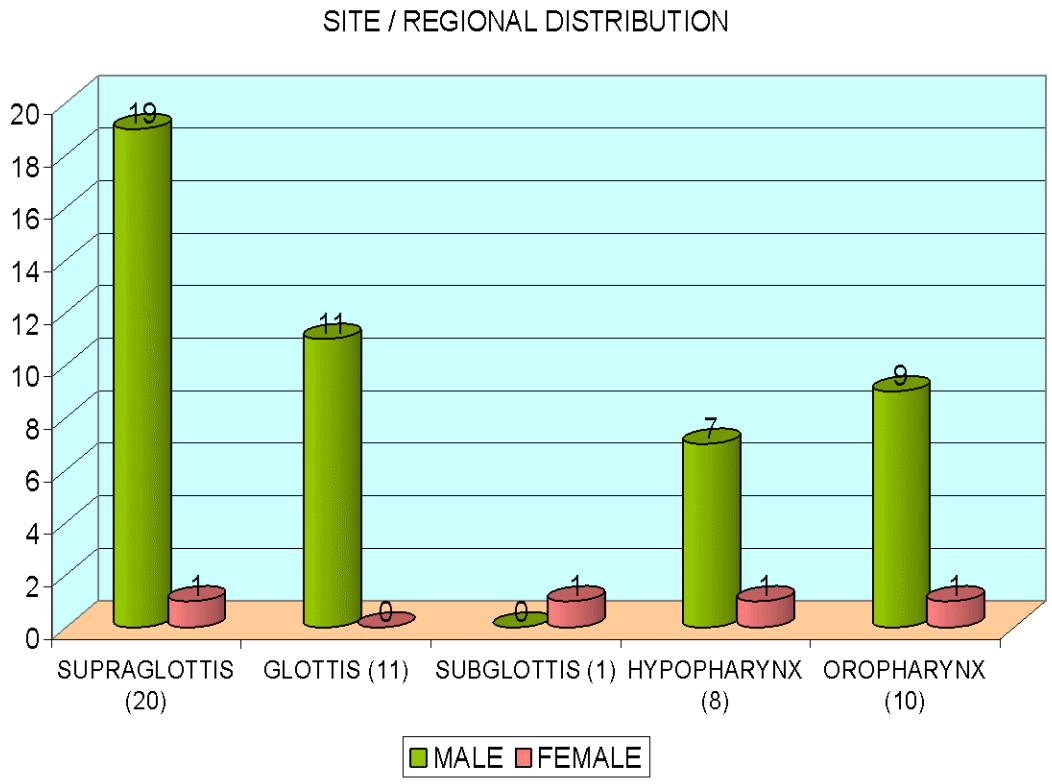

SITE / REGIONAL DISTRIBUTION
20
18
16
14
12
10
8
6
4
2
0
19
1
11
0
0
1
7
1
9
1
SUPRAGLOTTIS (20)
GLOTTIS (11)
SUBGLOTTIS (1)
HYPOPHARYNX (8)
OROPHARYNX (10)
MALE
FEMALE

TABLE 4

TUMOR STAGE	NUMBER OF PATIENTS	MEAN SERUM LDH LEVELS IU/L – PRE TREATMENT
T1	5	286
T2	15	367.53
T3	24	312.37
T4	6	363.66

In the study group t1 tumors have a mean serum LDH level of 286 IU/L , t2 tumors have 367.53 IU/L , t3 have 312.37 IU/L and t4 have 363.66 IU/L

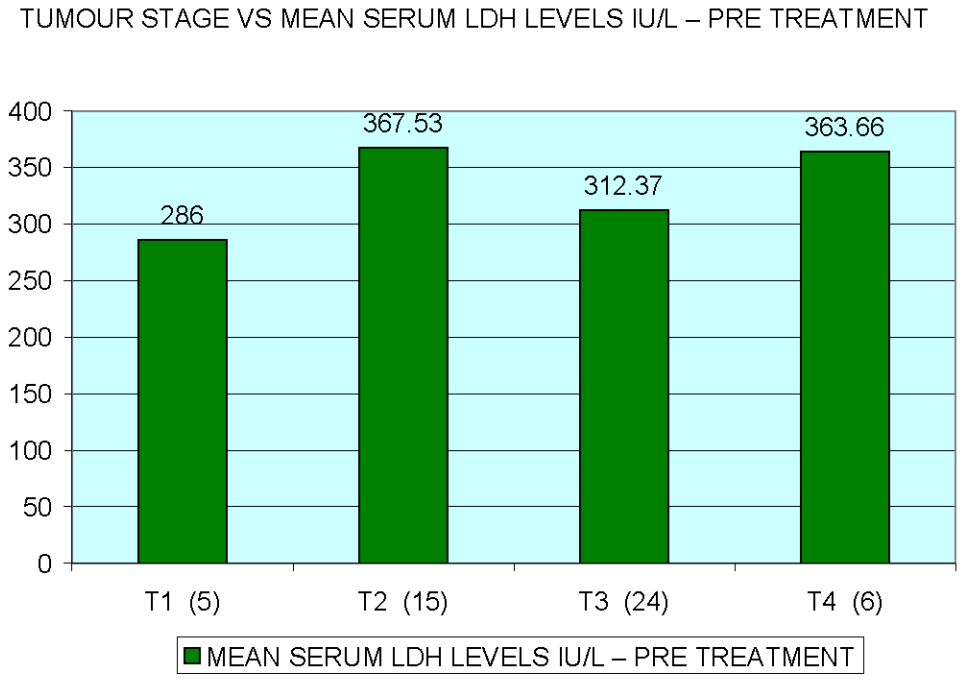


TABLE 5

TUMOR DIFFERENTIATION	TOTAL	PERCENTAGE	MEAN PRE TREATMENT SERUM LDH LEVELS IU/L
WELL DIFFERENTIATED	16	32%	312.875
MODERATELY DIFFERENTIATED	27	54%	327.07
POORLY DIFFERENTIATED	7	14%	393.14
P value			< 0.001 Significant

Most of the patients have moderately differentiated carcinoma 54% followed by well differentiated tumors 32% and poorly differentiated tumors 14% .Their mean serum LDH levels are 312.88 % , 327.07 % and 393 .14 % respectively.

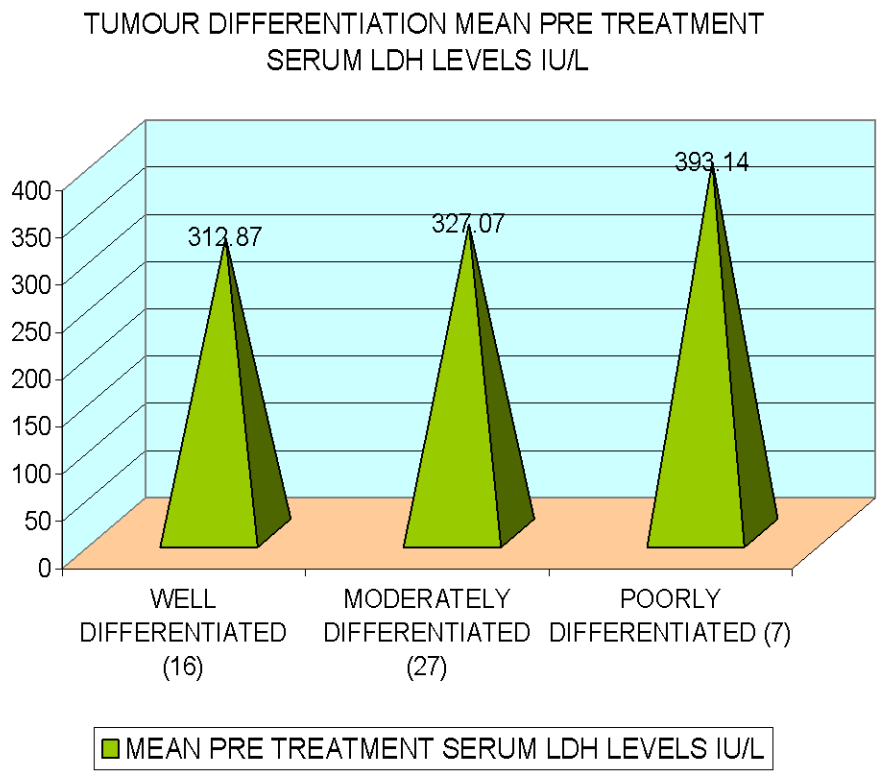

TUMOUR DIFFERENTIATION MEAN PRE TREATMENT SERUM LDH LEVELS IU/L
400
350
300
250
200
150
100
50
0
312.87
327.07
393.14
WELL DIFFERENTIATED (16)
MODERATELY DIFFERENTIATED (27)
POORLY DIFFERENTIATED (7)
MEAN PRE TREATMENT SERUM LDH LEVELS IU/L

TABLE 6

TREATMENT MODALITY	NUMBER OF CASES	MEAN OF SERUM LDH LEVELS IU/L		P value
		PRE TREATMENT	POST TREATMENT	
RADIOTHERAPY	47	331.92	206.42	< 0.001 Significant
SURGERY	3	343	240.66	< 0.001 Significant

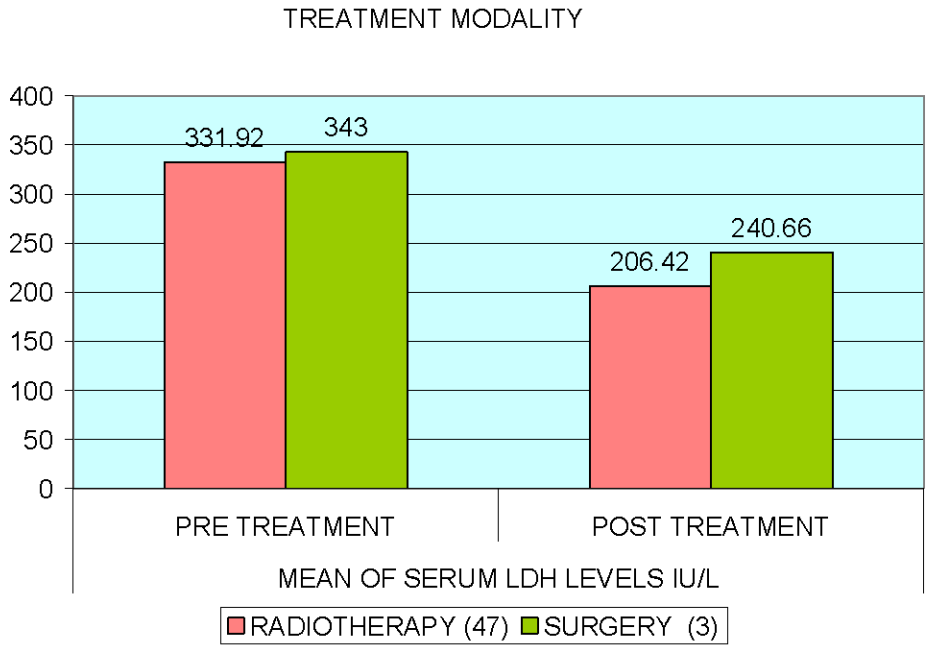
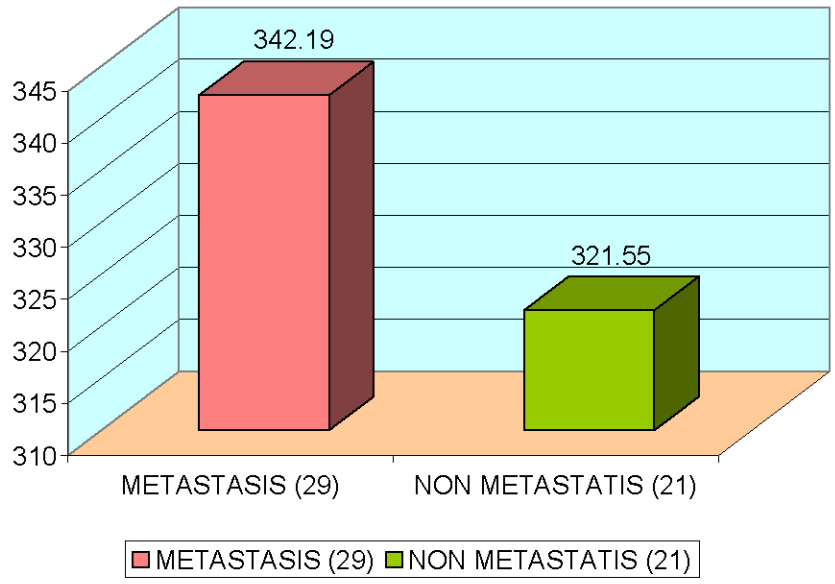


TABLE 7

	NUMBER OF PATIENTS	MEAN SERUM LDH LEVEL IU/L
METASTASIS	29	342.19
NON METASTATIS	21	321.55

MEAN SERUM LDH LEVEL IU/L FOR METASTASIS VS NON METASTASIS



DISCUSSION

The study includes 50 proven cases of head and neck malignancy and 50 controls. The study has been conducted in department of ENT, MADURAI MEDICAL COLLEGE, from August 2016 to July 2017.The control group included 40 males and 10 female patients who attended ENT out patient department for all other ailment other than head and neck squamous cell carcinoma. In the control group mean age among males was 58 years and their mean serum LDH levels showed 236 IU/litre. Among female, mean age was 50 years and mean serum LDH value was 198 IU/litre.

The study group includes 50 cases among which 46 patients were males and 4 were females. All females were non smokers and non alcoholic. Except for 1 female patient neuroendocrine carcinoma of larynx, others were tobacco and betel leaf chewers with or without betel leaf quid occasionally. Among 50 cases of proven head and neck squamous cell carcinoma, majority were supra glottis carcinoma, sub glottis carcinoma was rare. T3 stage was predominant followed by T2stage. Based on differentiation , moderate differentiation is of higher in number followed by well differentiated and poorly differentiated tumours

Among 50 patients, 29 had nodal metastasis. Their mean serum LDH was 342.19 IU/l. 21 patients who did not develop nodal metastasis showed their mean serum LDH value to be 321.53 IU/ litre.

The study includes 50 proven cases of head and neck squamous cell carcinoma among which 10 cases are carcinoma oropharynx, 20 cases are proven carcinoma supraglottis, 11 cases are carcinoma glottis, 1 patient belong to carcinoma sub glottis category, 8 patients are carcinoma hypopharynx

OROPHARYNX

Among ten cases of carcinoma oropharynx, only one belongs to female sex. She proved poorly differentiated squamous cell carcinoma. T staging T2 and nodal status N1. No clinical evidence of metastasis. Her USG abdomen and chest x ray PA view proved normal. CT scan showed growth in posterior one third tongue. Her pre treatment serum LDH was 402.24 IU/litre. Post radiotherapy serum LDH came as 198.11 IU/litre. All other nine cases were males. Among which five were well differentiated squamous cell carcinoma of oropharynx. Four belong to moderately differentiated squamous cell carcinoma category. Only one patient belongs to T4 staging. Among the cancer patients of oropharynx, seven were chronic smokers and alcoholics, two were chronic smokers alone. Female had tobacco chewing history.

SUPRAGLOTTIS

20 patients were proven carcinoma supraglottis. Among 20 patients, only one was female, aged 28 years proven neuro endocrine tumour of larynx moderately differentiated belong to T3 stage III category. She underwent total laryngectomy with thyroidectomy. Her pretreatment level was 347.24 and postsurgical value dropped to 248. Remaining 19 patients were males, among which 1 patient underwent surgery, whose pretreatment values was 380 and post treatment value 288.65. Among the 19 patients other than females, 5 were well differentiated head and neck squamous cell carcinoma. 10 patients belonged to moderately differentiated squamous cell carcinoma. 4 patients were of poorly differentiated squamous cell carcinoma. Among well differentiated group, 1 patient belongs to T1, 2 were T2, 2 were T3. Only one patient was a chronic smoker and alcoholic. Among the 10 moderately differentiated group, 5 patients were T2 , 4 patients T3, 1 patient T4.

4 patients were of poorly differentiated group. 1 patient T3, 3 patients T4.

From supraglottic tumour, pre treatment and post treatment values we arrived at a conclusion that pre treatment serum LDH was higher and dropped to lower values after treatment whatever may be the modality of management, surgery or radiotherapy. One another factor which has been arrived at is T4 stage showed increased pre treatment serum LDH value than

T1 stage. Similarly pre treatment serum LDH value showed a progressive increase and when we move through T1 to T4. That shows serum LDH increases with increase in tumour staging. Also seen poorly differentiated tumours showed high serum LDH values than moderate and well differentiated tumours. Except female patients in carcinoma supra glottis, all others were chronic smokers and alcoholics. Only duration and quantity of exposure varies.

GLOTTIS

Out of 11 cases of proven carcinoma glottis, 1 patient 50 years male, who is a proven moderately differentiated carcinoma T3 stage whose pre treatment value was 302 IU/litre and post surgical value was 186 IU/litre. He underwent total laryngectomy with partial thyroidectomy. Among the remaining 10 cases, 5 were well differentiated, 4 were moderately differentiated, 1 poorly differentiated. Among 11 cases 6 were T3, 3 were T2, 1 belongs to T1. Among the 11 patients only 6 were chronic smokers and alcoholics, remaining 5 were occasional smokers and social alcoholics.

CARCINOMA SUB GLOTTIS

Only one female among the 50 patients proved to be squamous cell carcinoma sub glottis. Staging T2N0M0 moderately differentiated

squamous cell carcinoma. Her pre treatment serum LDH showed 359.11IU/litre and post treatment was 220.16. She was not a tobacco chewer or an alcoholic.

CARCINOMA HYPOPHARYNX

9 cases of carcinoma hypopharynx was studied. Only 1 was female patient with moderately differentiated squamous cell carcinoma. Tumour staging was T2. Her pre treatment LDH showed 386.26IU/litre and post treatment 160.18 IU/litre. Only one patient belongs to T4Bstage, 3 patients were of T3 stage, 4 patients belonged to T2 stage. This shows tumours of hypopharynx present for treatment at a relatively advanced stage. Presentation at T1stage was rare. Patient usually comes for treatment when symptoms of dysphagia progresses. Commonest presentation of CA hypopharynx is T2 stage with no node. Pyriform sinus tumour present with cervical lymphadenopathy than with any other subsite.

Head and neck tumours are common in INDIAN sub continent. In the above study, percentage of carcinoma supra glottis is common followed by carcinoma oropharynx, carcinoma glottis, hypopharynx and last sub glottis. Average age of malignant tumors in male is 60 years and female it is 47 years. The reason for which male being more commonly affected than female is increased habit of smoking, alcohol with tobacco chewing in males compared with females. Symptoms with which head and neck

malignant tumour patients presented to OPD includes dysphagia, change in voice, difficulty in breathing, hoarseness of voice, cervical lymphadenopathy.

Out of the 50 patients in this study, totally 3 patients underwent surgery, remaining 47 underwent radiotherapy. There is no difference in serum LDH reduction level in both surgery and radiotherapy patients. Similarly for well, moderately or poorly differentiated tumours also the reduction in serum LDH level showed no correlation with the differentiation or stage of tumour.

Malignancies of head and neck constitute 50 – 70 % of cancers diagnosed in INDIA . The overall survival rate for some subsites is less. The poor survival is contributed to late presentation , poor accessibility ,lack of awareness. The key factor in increasing survival is early detection and treatment of the disease and recurrence . This study attempts to enlighten a parameter that would facilitate the above idea.

In the present study of head and neck squamous cell carcinoma ,the mean serum LDH level in control group was 236 IU/L for males and 198 IU/L for females. This is within the normal lab control of 120 – 246 IU/L. in the study group the pre treatment level of serum LDH was 331.92 IU/L for radiotherapy group and 343 IU/L for surgery group .These values are grossly above the normal level. The post treatment values of serum

LDH for radiotherapy and surgery group are 206.42 IU/L and 240.66 IU/L respectively. These values are within the normal lab control values.

This proves the fact that serum LDH is elevated in patients with head and neck malignancy .The study shows serum LDH levels decrease to normal level following curative therapy irrespective of the modality of therapy.

From this study we also see the pre treatment LDH levels vary with the degree of differentiation of tumor. the well differentiated tumors have mean serum LDH levels of 312.88 IU/L, moderately differentiated 327.07 IU/L, poorly differentiated tumors 393.14 IU/L. this shows the levels increase with increasing grades of tumor.

Another factor derived from the study is serum LDH levels also correlate with size of the tumor .t2 stage exhibit a mean of 367.53 IU/L compared to t1 stage which showed mean of 286 IU/L pre treatment. Similarly t4 stage showed pre treatment mean of 363.66 IU/L compared to 312.37 IU/L in t3. Serum LDH seems to correlate with size of the tumor as larger tumor have more cells from which enzymes might leak into blood or larger necrotic fraction so that the enzymes leak into blood as a result of cell break down.

One other interesting factor to emerge from the study is serum LDH levels also correlate with dissemination of disease. The levels are higher in patients having metastasis to cervical node than those with No neck. In this study 29 patients had cervical node metastasis clinically and none of the patients had systemic metastasis which is also uncommon in head and neck cancers.remaining 21 patients had no clinical and radiologically detectable metastasis. The serum LDH levels for metastatic group was 342.19IU/L and for non metastatic group was 321.55IU/L . Other serum enzymes like serum adenosine deaminase and phosphate hexose isomerase does not show this correlation.

CONCLUSION

From this study, the following conclusions are arrived

1] Serum LDH is consistently elevated in head and neck squamous cell carcinomas.

2] The rise in serum level is irrespective of the site of origin of tumor.

3] The enzyme increase in other histological types is not evaluated in this study

4] The rise in enzyme level increases with the size of the tumor and shows higher levels in larger tumors compared with smaller ones.

5] The serum LDH levels also correlate with the histological grade of malignancy . Poorly diifferentiated carcinoma shows largest level followed by moderately differentiated and then well differentiated tumors.

6] The levels are significantly higher in patients with metastasis than those without metastasis.

7] From this study it is concluded that serum LDH levels decrease to within normal range in patients treated by curative therapy . All patients show significant fall in levels following radiotherapy or surgery.

8] The fall in level is irrespective of the curative treatment modality.

9] Morphological type of tumor does not show any correlation with enzyme levels

10]As the enzyme level falls with therapy ,this could be used for follow up of the patient to detect recurrences.

11]This test can be used to screen high risk patients at primary care level since the procedure is easy and cost effective.

It is said cancer is very easy to see than to foresee. By periodically screening persons with risk factors with simple procedures malignant changes can be detected at incipient stage. When a malignancy is still cytological than histological cure can be given. Smoking and alcohol were found to be the main etiological factors. Health education and periodic screening will help early detection of head and neck malignancy and will go a long way in men's quest to weed out diseases and improve the quality of life .

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PROFORMA

PATIENT DETAILS

NAME AGE/SEX IP NO

ADDRESS

OCCUPATION INCOME

SOCIOECONOMIC STATUS

PRESENTING COMPLAINTS

Difficulty in swallowing

Pain during swallowing

Difficulty in breathing

Change in voice

Ear pain

Fever

Cough

Hemoptysis

Loss of weight

Loss of appetite

Throat pain

Neck swelling

Aspiration

PAST HISTORY

Similar illness in past

Previous surgery

Diabetes ,hypertension, tuberculosis

White patches in oral cavity

PERSONAL HISTORY

Smoking – beedi /cigarette/cigars per day

Alcohol – ml / years

Snuff

Betel nut chewin

FAMILY HISTORY

GENERAL EXAMINATION

LOCAL EXAMINATION

ORAL CAVITY

Lips

Teeth

Anterior two third tongue movements

Floor of mouth

Vestibule, gingivobuccal sulcus

OROPHARYNX

Tonsil

Soft palate movements

Posterior one third tongue

Tonsillolingual sulci

Retromolar trigone

Posterior pharyngeal wall

Gag reflex

LARYNGOPHARYNX

INDIRECT LARYNGOSCOPY

Base of tongue

Pharyngoepiglottic fold

Aryepiglottic fold

Arytenoids

False and true cords

Pyriform sinuses

Posterior pharyngeal wall

Mobility of larynx

NOSE

External nose

Septum

Vestibule

Mucosa ,meatus,

Floor

Turbinates

Sinus tenderness

POST NASAL EXAMINATION

Posterior end of septum

Tubal elevation

Roof of nasopharynx

Posterior end of turbinates

EXAMINATION OF NECK

Laryngeal crepitus

External laryngeal framework

Tenderness

Node – level ,size, side , number [fixity excluded as TNM staging does not include fixity as criteria]

EXAMINATION OF RESPIRATORY SYSTEM

Tracheal position

Breath sounds

EXAMINATION OF CARDIVASCULAR SYSTEM

EXAMINATION OF ABDOMEN

PROVISIONAL DIAGNOSIS

INVESTIGATIONS

1]BLOOD -Total count

Differential count , Hemoglobin%

Renal function test

Lactate dehydrogenase

2]urine

Albumin,sugar,Deposits

3]chest x ray PA view

4]x-ray neck – AP , lateral view

5]ultrasonogram

6]computerized tomography

7]endoscopy

8]biopsy – histological type

_grade and differentiation of tumor

_invasive margin

DIAGNOSIS

PLAN OF MANAGEMENT

RADIOTHERAPY AND OR SURGERY

FOLLOW UP

FULL CLINICAL EXAMINATION

SERUM LACTATE DEHYDROGENASE LEVELS

S.No	Name	Age	Sex	IP.No	CA	Histological Type (Differentiation)	TNM Staging	USG Abdomen	Chest X - Ray PA view	CT - Scan	Treatment modality	Pre - treatment Serum LDH IU/L	Post - treatment Serum LDH IU/L
1	Alagan	55	M	112042	Oropharynx	Well	$T_2N_0M_0$	N	N		Radiotheraphy	380.42	220.80
2	Muthumani	55	M	113861	Oropharynx	Well	$T_2N_0M_0$	N	N		Radiotheraphy	356.80	200.34
3	Sankaranarayanan	61	M	1145665	Oropharynx	Well	$T_2N_0M_0$	N	N		Radiotheraphy	345.60	240.00
4	Vijaya	55	F	57446	Oropharynx	Poorly	$T_2N_1M_0$	N	N		Radiotheraphy	402.24	198.11
5	Sundarambal	55	F	596443	Oropharynx	Well	$T_2N_1M_0$	N	N		Radiotheraphy	280.60	160.00
6	Subbaraj	54	M	60840	Oropharynx	Moderate	$T_2N_1M_0$	N	N		Radiotheraphy	302.12	180.00
7	Ashokkumar	43	M	5012	Oropharynx	Moderate	$T_3N_1M_0$	N	N		Radiotheraphy	304.00	196.42
8	Alagesan	31	M	7001	Oropharynx	Moderate	$T_1N_0M_0$	N	N		Radiotheraphy	260.80	180.00
9	Balasubramanian	65	M	59684	Oropharynx	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	406.34	260.00
10	Muniyandi	61	M	112163	Oropharynx	Well	$T_{4a}N_1M_0$	N	N	Growth posterier-1/3 tongue extending to hard palate	Radiotheraphy	284.00	190.22
11	Ramaraj	41	M	7094	Supraglottis	Moderate	$T_3N_1M_0$	N	N		Radiotheraphy	342.21	220.00
12	Veeranan	70	M	3412	Supraglottis	Moderate	$T_2N_0M_0$	N	N	Tumor involving epiglottis extending to ® AE fold & ® vocal card	Radiotheraphy	286.14	190.00
13	Kasiesaran	36	M	32497	Supraglottis	Well	$T_2N_0M_0$	N	N		Radiotheraphy	290.24	180.00

14	Kumarasamy	63	M	9022	Supraglottis	Moderate	$T_4N_1M_0$	N	N	Tumor involving (L) AE fold & invades thyroid	Radiotheraphy	304.00	198.00
15	Sikkandar	65	M	7281	Supraglottis	Well	$T_3N_0M_0$	N	N		Radiotheraphy	302.26	220.00
16	Kaleeswari	28	F	677175	Supraglottis	Moderate	$T_3N_0M_0$	N	N	differentiated Neuroendocrine tumor of larynx	SURGERY	347.24	248.00
17	Paramasivam	65	M	112864	Supraglottis	Well	$T_1N_0M_0$	N	N		Radiotheraphy	304.04	216.00
18	Sridaran	52	M	67847	Supraglottis	Poorly	$T_{4a}N_0M_0$	N	N		Radiotheraphy	410.82	268.00
19	Kumaravel	45	M	2939	Supraglottis	Well	$T_3N_0M_0$	N	N		SURGERY	380.00	288.65
20	Ramar	63	M	28517	Supraglottis	Moderate	$T_2N_0M_0$	N	N	Tumor involving ® AE fold & extends into glottis	Radiotheraphy	386.00	347.18
21	Chellaiah	55	M	2677	Supraglottis	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	404.00	315.14
22	Vasagan	57	M	1144958	Supraglottis	Poorly	$T_3N_1M_0$	N	N		Radiotheraphy	386.41	198.00
23	Natarajan	65	M	56086	Supraglottis	Well	$T_2N_0M_0$	N	N	Tumor involving ® AE fold & extends into ® pyriform sinus	Radiotheraphy	292.00	168.00
24	Meyyan	58	M	1120283	Supraglottis	Moderate	$T_3N_1M_0$	N	N		Radiotheraphy	300.00	210.00
25	Muniyandi	64	M	1144650	Supraglottis	Moderate	$T_2N_1M_0$	N	N		Radiotheraphy	260.18	194.00
26	Karuppaiah	65	M	31875	Supraglottis	Moderate	$T_3N_0M_0$	N	N		Radiotheraphy	264.00	200.00
27	Ramu	63	M	60814	Supraglottis	Moderate	$T_3N_1M_0$	N	N		Radiotheraphy	272.11	164.00
28	Malaisamy	58	M	7386	Supraglottis	Poorly	$T_4N_{2b}M_0$	N	N	Tumor involving epiglottis ® AE fold with thyroid cartilage invasion	Radiotheraphy	414.34	236.00
29	Paramasivam	65	M	3861	Supraglottis	Poorly	$T_4N_1M_0$	N	N		Radiotheraphy	426.00	220.41
30	Kandhasamy	65	M	9084	Supraglottis	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	386.46	240.00

31	Kalandhaisamy	65	M	114061	Glottis	Poorly	$T_3N_1M_0$	N	N		Radiotheraphy	304.84	238.42
32	Jayaraman	55	M	54923	Glottis	Moderate	$T_3N_0M_0$	N	N		Radiotheraphy	296.00	196.00
33	Anwar Beck	65	M	1146806	Glottis	Well	$T_1N_0M_0$	N	N	Tumor involves both VC and anterior commissure.	Radiotheraphy	284.82	174.00
34	Balasubramanian	65	M	56341	Glottis	Well	$T_3N_0M_0$	N	N		Radiotheraphy	274.00	140.00
35	Jayachandran	50	M	4233	Glottis	Moderate	$T_3N_0M_0$	N	N		SURGERY	302.00	186.00
36	Jayapal	48	M	71107	Glottis	Well	$T_1N_0M_0$	N	N		Radiotheraphy	286.00	140.11
37	Murugan	70	M	5309	Glottis	Moderate	$T_3N_0M_0$	N	N		Radiotheraphy	347.65	220.00
38	Pitchai	62	M	31798	Glottis	Well	$T_1N_0M_0$	N	N		Radiotheraphy	296.00	198.24
39	Murugesan	72	M	7841	Glottis	Moderate	$T_3N_0M_0$	N	N		Radiotheraphy	306.00	186.44
40	Mani		M	9842	Glottis	Moderate	$T_3N_0M_0$	N	N		Radiotheraphy	312.00	190.26
41	Mariyappan		M	8064	Glottis	Well	$T_2N_0M_0$	N	N	Tumor involves both VC and extends into ® AE fold	Radiotheraphy	315.00	200.00
42	Pandiyammal	55	M	8042	Glottis	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	359.11	220.24
43	Velsamy	57	M	31572	Hypopharynx	Well	$T_2N_0M_0$	N	N	Tumor involving® pyriform sinus & extends to post cricoid region	Radiotheraphy	312.44	182.24
44	Selvaraj	58	M	31476	Hypopharynx	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	304.41	168.00
45	Manivannan	44	M	30689	Hypopharynx	Poorly	$T_3N_1M_0$	N	N	Tumor involvs(L) pyriform sinus extends to (L) AE fold &(L) vocal card	Radiotheraphy	410.24	220.12
46	Ramamoorthy	60	M	1144985	Hypopharynx	Moderate	$T_{4b}N_{2c}M_0$	N	N	Tumor involvs(L) pyriform sinus with invasion of thyroid cartilage	Radiotheraphy	344.48	180.00

47	Selvarani	49	F	56817	Hypopharynx	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	386.26	160.18
48	Sivan	55	M	56423	Hypopharynx	Moderate	$T_2N_0M_0$	N	N		Radiotheraphy	306.12	184.00
49	Subbukalai	58	M	673942	Hypopharynx	Moderate	$T_3N_1M_0$	N	N		Radiotheraphy	315.00	220.00
50	Dharmaraj	60	M	722314	Hypopharynx	Moderate	$T_3N_1M_0$	N	N		Radiotheraphy	427.15	240.00

MADURAI MEDICAL COLLEGE

MADURAI, TAMILNADU, INDIA -625 020

(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.G.Manimala
Course	:	PG in MS., Otorhinolaryngology
Period of Study	:	2015-2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A Comparative study on Evaluation of Serum LDH in management of Head and Neck squamous cell carcinoma
Ethical Committee as on	:	17.03.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary

Chairman
Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

Dean / Convenor
DEAN
Madurai Medical College
Madurai-20

URKUND

Urkund Analysis Result

Analysed Document: DR. MANIMALA DISSERTATION ENT - MAY 2018 FOR PLAGIARISM.doc (D31225674)
Submitted: 10/11/2017 6:18:00 PM
Submitted By: drgmala86@gmail.com
Significance: 2 %

Sources included in the report:

siddharth.docx (D31156127)
amutha thesis.docx (D30979644)

Instances where selected sources appear:

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